Chlamydia Pneumoniae Exposure and Inflammatory Markers in Acute Coronary Syndrome (CIMACS)

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Previous studies have shown higher levels of *Chlamydia pneumoniae* (*C. pneumoniae*, CP) antibody titers (CPIgG), C-reactive protein (CRP), and fibrinogen in patients with coronary artery disease. The role of these infectious and inflammatory markers in precipitating acute coronary syndrome (ACS) is unclear. We conducted a cross-sectional study on patients (n = 830, mean age 63 ± 15 years, 57% male) admitted to the chest pain center of our institution. The differences in the CPIgG, CRP, and fibrinogen levels in patients who were diagnosed with ACS versus those who were not (non-ACS) were evaluated. CPIgG titers tended to be higher in the ACS group than in the non-ACS group. However, when different titers were used to define seropositivity, the difference achieved statistical significance only at the titer of ≥1:1,024 (35% vs 26%, p = 0.004). CRP (median 0.48 vs 0.33 mg/dl, p <0.0001), fibrinogen (median 317 vs 293 mg/dl, p <0.0001), and leukocyte count (median 7.7 vs 6.9 10^9/L, p <0.0001) were higher in the ACS group. On multivariate analysis, CPIgG ≥1:1,024 (odds ratio [OR] 1.62), diabetes (OR 1.91), hypertension (OR 1.46), prior myocardial infarction (OR 1.78), smoking (OR 1.70), Caucasian race (OR 1.7), high-density lipoprotein (OR 0.98), and elevated troponin-T (OR 12.44) were the only factors independently associated with ACS. Thus, we found a strong association between high level seropositivity to CP and ACS. This may indicate recent re-infection or an exaggerated immune response to CP as an etiologic factor for ACS. This study also suggests that therapeutic interventions may need to be specifically targeted to these patients. ©2001 by Excerpta Medica, Inc.

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The role of *Chlamydia pneumoniae* (*C. pneumoniae*, CP) in coronary artery disease is controversial.[1–7] Although the presence of CP in many atherosclerotic lesions is no longer disputed, the exact nature of the association between the organism and atherosclerosis is unclear. There is increasing evidence that inflammatory and immune processes play a pathogenetic role in coronary artery disease.[8] We conducted an observational study in patients presenting to the chest pain center of a tertiary care hospital to evaluate the seroprevalence of antibody titers against CP in the population and to determine whether it was different in patients who were subsequently proved to have acute coronary syndrome (ACS). We also investigated the association between antibody titers against CP and inflammatory markers, including C-reactive protein (CRP), fibrinogen and leukocyte count, and troponin-T.

METHODS

Study design: A cross-sectional study was designed to evaluate antibodies against CP and markers of inflammation in patients with and without ACS.

Patients: Patients were enrolled from the chest pain center, which evaluates and treats all patients presenting to the emergency department of a tertiary care center, with clinical history and symptoms suggestive of ACS. Eight hundred thirty patients were enrolled in this study between March 1999 and June 1999. This constituted 64% of all patients presenting to the center during this time period (1,304). Exclusion criteria were: age <18 years, any malignancy requiring treatment within the previous 2 months, acquired immunodeficiency syndromes, chronic steroid use, immunosuppressive therapy (e.g., for transplant), chronic liver disease, inflammatory bowel diseases, rheumatoid arthritis, systemic lupus erythematosis, and any major surgery within the past 2 months. Patients with multiple visits during the period were enrolled at their initial visit.

Evaluation: All patients were evaluated by the emergency department physicians or cardiology nurse clinicians. Clinical information regarding age, gender, ethnicity, medical history of hypertension, hyperlipidemia, current smoking, smoking (past or current), diabetes, coronary artery disease, congestive heart failure, and previous myocardial revascularization (percutaneous transluminal coronary angioplasty and/or coronary artery bypass surgery) were obtained. Duration of symptoms before the hospital visit was recorded. History regarding symptoms of respiratory illnesses during the previous 6 months as well as the use of any prescription antibiotics during the same period was ascertained. All patients received standard

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TABLE 1 Distribution of Clinical Variables in the Study Sample (n = 830) and Their Univariate Association With Acute Coronary Syndrome (ACS)

Clinical Variables	All Patients (n = 830)	No ACS (n = 412)	ACS (n = 418)	P Value
Age (yrs) (mean ± SD)	63.3 ± 14.7	61 ± 16	65 ± 13	0.0002
Men	469 (56.6%)	208 (51%)	260 (63%)	0.001
Caucasian race	689 (83.5%)	322 (79%)	366 (88%)	0.002
Systemic hypertension*	506 (62.2%)	219 (54%)	286 (70%)	0.001
Hyperlipidemia†	330 (40.6%)	145 (36%)	185 (45%)	0.005
Diabetes mellitus	182 (22.4%)	58 (14%)	124 (30%)	0.001
Coronary artery disease‡	363 (44.7%)	141 (35%)	222 (55%)	0.001
Congestive heart failure	88 (10.8%)	41 (10%)	46 (11%)	NS
Prior myocardial infarction	262 (32.3%)	97 (24%)	164 (40%)	0.001
Prior percutaneous coronary intervention	177 (21.7%)	70 (17%)	107 (26%)	0.002
Prior coronary bypass	155 (19%)	52 (13%)	103 (25%)	0.001
Current smoker	124 (15.4%)	59 (15%)	65 (16%)	NS
Ever smoked§	420 (51%)	172 (42%)	248 (59%)	<0.0001
Symptom duration (h) (mean ± SD)	4.73 ± 9.15	4.90 ± 9.14	4.56 ± 9.17	NS

*Systolic blood pressure >160 mm Hg or a diastolic pressure of >90 mm Hg or use of antihypertensive medication.
†Total cholesterol of >240 mg/dl or use of pharmacologic therapy.
‡Angiographic evidence of >50% lesion in ≥1 coronary artery or evidence of myocardial ischemia on noninvasive testing.
§>10 pack-year smoking anytime in the past.

medical care as per the chest pain center protocol or at the discretion of their attending physician.

Laboratory tests: Apart from the routine blood tests, which included complete blood count, serum electrolytes, serum urea nitrogen, creatinine, and cardiac enzymes (creatine kinase [CK] and CK-MB), the patients had additional venous blood samples drawn simultaneously for the study. Immunoglobulin-G (IgG) and IgM antibodies against CP (CPIgG and CPIgM) were measured using microimmunofluoresent assay at an outside facility (ARUP Labroratory, Salt Lake City, Utah). CK, CK-MB, and troponin-T were measured using an electrochemiluminescence immunoassay (ROCHE Elecsys 1010/2010, Tokyo, Japan). CRP levels were determined by a high sensitivity commercial assay (Dade Behring BN II System, Newark, Delaware). Fibrinogen was measured using the MDA 180 method (Organon Teknika MDA Coagulometer, Oklahoma City, Oklahoma).

Outcomes: Chest pain etiology was ascertained by blinded chart review. ACS included myocardial infarction, unstable angina, and probable unstable angina. Myocardial infarction was identified by abnormal cardiac enzyme levels (twofold increase in total CK enzyme with ≥3.9% CK-MB) along with either sustained chest discomfort or electrocardiographic changes. Troponin-T levels were not used for the diagnosis of ACS. Unstable angina was defined as chest discomfort with or without electrocardiographic changes, along with noninvasive (Sestamibi/2-dimensional echocardiographic) evidence of ischemia or angiographic evidence of significant (≥70%) coronary artery disease. Probable unstable angina was identified by symptoms of chest discomfort, with electrocardiographic changes but with no further noninvasive or invasive workup performed. Patients who did not have ACS (non-ACS) included: (1) those diagnosed as having a noncardiac etiology for their current hospital visit with no evidence of ACS (noncardiac chest pain); (2) patients with known history of coronary artery disease but no evidence of ACS (ischemic heart disease); and (3) patients who presented primarily because of valvular disease, arrhythmia, or congestive heart failure but had no evidence of ACS ("other" heart disease).

Statistical analysis: Normally distributed continuous variables were compared using the *t* test. Categorical variables were compared using chi-square test. IgG antibody titers were analyzed both as a continuous variable (using the reciprocal titer) and as a dichotomous variable at different levels, i.e., <1:64 versus ≥1:64, <1:128 versus ≥1:128, <1:128 versus ≥1:128, <1:512 versus ≥1:512, <1:1,024 versus ≥1:1,024 (instead of using an arbitrary definition of seropositivity). The distribution of the reciprocal values of CPIgG were also compared using Wilcoxon's rank-sum test and presented as medians. Due to skewed distribution of CRP, fibrinogen, and leukocyte count, log normalization was performed. Geometric means were compared using the *t* test for 2 groups and 1-way analysis of variance for multiple groups. Their distributions were also compared using Wilcoxon's rank-sum test for 2 groups and Kruskal-Wallis 1-way analysis of variance for multiple groups and presented as medians. $\alpha = 0.05$ was used for statistical significance except for multiple separate end point analysis of CPIgG titers, where a corrected $\alpha = 0.01$ was used. Multivariate logistic regression was performed using ACS as the dependent variable. Independent variables included all variables found to have statistically significant association with ACS on univariate analysis (CPIgG was used both as a continuous and dichotomous variable). Association between CPIgG titers and inflammatory markers were analyzed using both parametric (1-way analysis of variance) and nonparametric tests (Kruskal-Wallis 1-way analysis of variance). Data analyses were facilitated by using SAS software (version 6.12, SAS Institute, Cary, North Carolina).

The study was approved by the institutional Human Investigation Committee. All patients provided informed consent.

RESULTS

The baseline demographic characteristics and distribution of coronary risk profile (Table 1) shows a study population at a high risk for coronary artery disease and ACS. Overall, 418 patients (50%) were diagnosed with ACS, including 113 (14%) with new myocardial infarction, 281 (34%) with unstable angina, and 24 (3%) with probable unstable angina. Four

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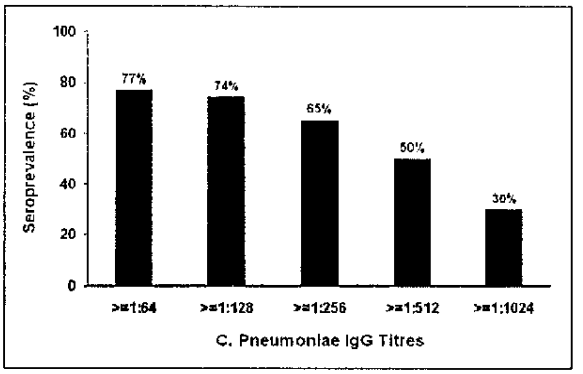

FIGURE 1. Seroprevalence of CPIgG titers in the study population (n = 796): 77% of the patients in the study sample had a CPIgG titer ≥1:64, 74% were ≥1:128, 65% were ≥1:256, 50% were ≥1:512, and 30% were ≥1:1,024.

TABLE 2 Univariate Association Between Acute Coronary Syndrome (ACS) and *Chlamydia Pneumoniae* (CP) Antibodies

CPIgG Antibody Titers (CPIgG)	No ACS (n = 386)	ACS (n = 410)	p Value*	Odds Ratio (99% CI)
Mean of the reciprocal CPIgG titer	422	499	0.008	
Median of the reciprocal CPIgG titer	256	512	0.01	
CP titers				
CPIgG ≥1:64	318 (75%)	298 (79.7%)	0.25	1.21 (0.77–1.65)
CPIgG ≥1:128	299 (70.9%)	287 (76.8%)	0.1	1.30 (0.89–1.72)
CPIgG ≥1:256	259 (61.4%)	258 (69%)	0.04	1.35 (0.97–1.73)
CPIgG ≥1:512	196 (46.5%)	199 (53.2%)	0.13	1.24 (0.87–1.61)
CPIgG ≥1:1024	109 (25.8%)	132 (35.3%)	0.004	1.57 (1.17–1.97)

*Corrected $\alpha = 0.01$ only for multiple separate end point analysis of CPIgG.
CI = confidence intervals.

hundred twelve patients (50%) were diagnosed with non-ACS: 318 (38%) with noncardiac chest pain, 53 (7%) with ischemic heart disease, and 41 (5%) with other heart disease. On univariate analysis, the ACS group was older and had more men and Caucasians compared with the non-ACS group. The patients in ACS group also had a higher prevalence of hypertension, diabetes mellitus, hyperlipidemia, ever-smoking (but not current smoking), diagnosed coronary artery disease, history of ≥1 myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery. There was no difference between the groups in terms of symptom duration before presentation to the hospital.

Of the 796 patients for whom CPIgG titers were available, 180 (22.6%) were seronegative (CPIgG <1:64), 30 (3.8%) had a titer of 1:64, 69 (8.7%) had a titer of 1:128, 122 (15.3%) had a titer of 1:256, 154 (19.3%) had a titer of 1:512, and 241 had a titer of ≥1:1,024 (30.3%). Seventy-seven percent of the patients in the study sample had a CPIgG titer ≥1:64, 74% were ≥1:128, 65% were ≥1:256, 50% were ≥1:512, and 30% were ≥1:1,024 (Figure 1). Only 3 patients had an elevated CPIgM titer ≥1:40 consistent with acute infection; all 3 also had a CPIgG titer of ≥1:256. Male gender (mean reciprocal CPIgG 510 ± 415 vs 396 ± 390, p = 0.0001), history of coronary artery disease (mean reciprocal CPIgG 501 ± 418 vs 432 ± 396, p = 0.02), and having ever smoked (mean reciprocal CPIgG 498 ± 412 vs 424 ± 402, p = 0.01) were the only clinical variables found to be associated with antibody titers against CP. Recent symptoms of respiratory infections and use of antibiotics had no association with the CPIgG titers.

In general, CPIgG titers were higher in the ACS group compared with the non-ACS group (Table 2). The difference was statistically significant for CPIgG of ≥1:1,024 only. The inflammatory markers, including CRP, fibrinogen, and leukocyte counts, were significantly higher in the ACS group compared with the non-ACS group (Table 3). Also, a higher proportion of patients had troponin-T ≥0.2 ng/ml in the ACS group. Although total cholesterol and low-density lipoprotein cholesterol were not different between the groups, high-density lipoprotein cholesterol was significantly lower in the ACS group.

On multivariate analysis (Table 4) a CPIgG titer of ≥1:1,024 was an independent predictor of ACS (odds ratio 1.62, p = 0.01). Other variables that were found to be independently associated with the diagnosis of ACS were ever being a smoker, history of myocardial infarction, Caucasian race, low high-density lipoprotein cholesterol, hypertension, and elevated troponin-T at the time of admission. None of the inflammatory markers were found to be independently associated with ACS.

There was no association between CPIgG titers and the inflammatory markers (CRP, fibrinogen, and leukocytes) or troponin-T elevation in the study sample (Table 5). This lack of association persisted even when ACS and non-ACS groups were separately analyzed.

DISCUSSION

The present study is one of the largest population-based studies analyzing the association between CP and coronary artery disease. Unique aspects of this study include its focus on ACS and the study population that is very representative of patients at high risk for coronary artery disease. The study found a higher seroprevalence of IgG antibodies to CP, especially in the higher ranges, compared with earlier studies.[7,9,10] In contrast, acute infection with CP could be implicated only in 3 patients. A possible explanation for the high seroprevalence may be that the study population was older, had a higher prevalence of men, smokers, coronary artery disease, and other comorbidities. Age, gender, smoking, geographic location, socioeconomic status, dietary habits, and infections in general have been implicated in seropositivity to CP.[9,11] The present study did not evaluate socioeconomic status

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TABLE 3 Univariate Association Between Acute Coronary Syndrome (ACS), Inflammatory Markers, Troponin-T, and cholesterol

Variables	No ACS (n = 412)	ACS (n = 418)	p Value
CRP			
Geometric mean (mg/dl)	0.35	0.55	0.0001
Median (mg/dl)	0.33	0.48	<0.0001
Fibrinogen			
Geometric mean (mg/dl)	296	322	0.0003
Median (mg/dl)	293	317	<0.0001
Leukocyte count			
Geometric mean (10^9L)	7	7.9	<0.0001
Median (10^9L)	6.9	7.7	<0.0001
Troponin-T ≥0.2 ng/ml	8 (2%)	98 (24%)	<0.0001
Total cholesterol (mg/dl) (mean ± SD)	180 ± 42	177 ± 44	NS
Low-density lipoprotein (mg/dl) (mean ± SD)	110 ± 50	117 ± 74	NS
High-density lipoprotein (mg/dl) (mean ± SD)	48 ± 14	44 ± 14	0.0001

TABLE 4 Multivariate Analysis of Variables Associated With Acute Coronary Syndrome

Variables	Odds Ratio	p Value	95% CI
CP antibody titer CPIgG ≥ 1:1024	1.62	0.010	1.11, 2.35
Diabetes mellitus	1.91	0.003	1.25–2.91
Ever-smoked	1.70	0.003	1.20–2.41
Prior myocardial infarction	1.78	0.002	1.24–1.54
Caucasian race	1.70	0.029	1.06–2.72
High-density lipoprotein (mg/dl)	0.98	0.003	0.97–0.99
Systemic hypertension	1.46	0.040	1.01–2.11
Troponin-T ≥0.2 ng/ml	12.44	<0.0001	5.78–26.78

Abbreviation as in Table 2.

and dietary habits; we did, however, find CPIgG positively associated with male gender, history of coronary artery disease, and history of smoking. A recent study by Bartels et al[12] found a strong association between elevated IgG titers against CP and the presence of the bacterium in occluded vein grafts. This along with the reported stimulation of humoral response to CP by percutaneous coronary interventions[13] have raised the issue whether manipulation of atherosclerotic plaque makes hidden CP antigens accessible to the immune system. The present study did not find any association between CPIgG titers and a history of bypass surgery or percutaneous coronary interventions.

Inflammatory markers: ACS-CPIgG: CRP, fibrinogen, and leukocytes as markers of inflammation have not only been associated with coronary artery disease but have also been shown to be of prognostic significance.[3,14,15] The present study found a strong positive association between these markers and ACS on univariate analysis. However, on multivariate analysis, traditional risk factors and very high titers of CPIgG (≥1:1,024) were the only independently associated variables. This suggests that inflammatory markers are not independently associated with ACS but are only surrogates for the "triggers" of ACS. Toss et al[16] have shown an association between IgA antibodies to CP and fibrinogen and CRP, and Anderson et al[17] have shown an association between CRP and combined seropositivity to CP and *Helicobacter pylori*. This added to the plausible role of CP in the chronic inflammatory nature of atherosclerosis. The present study failed to demonstrate any association between inflammatory markers and antibody titers to CP. Several other studies have failed to show this association as well.[2,6,7]

Similarly, troponin-T has also been shown to be a prognostic factor in patients with coronary artery disease.[18,19] This study found a very strong and positive association between troponin-T measured at the time of admission and ACS, which was expected. Toss et al[16] did show a positive association between troponin-T and IgA antibodies to CP. However, the present study failed to show any such association between IgG antibodies to CP and troponin-T. This might be secondary to our inability to identify chronic and reinfected/reactivated cases of CP because IgA titers were not obtained.

CPIgG and ACS: The most significant finding of the present study was the association between very high titers of CPIgG and ACS. Earlier studies have shown a progressively stronger association between increasing antibody titers to CP with chronic as well as ACS.[1,20] Miettinen et al[21] reported a relation between antibodies to CP and acute coronary artery disease in nondiabetics but not in diabetics. It appears, therefore, that it is not the simple exposure to CP, but the way in which the infection is handled by the individual immune system (host-pathogen interaction) that affects ACS. Several investigators have suggested the role of autoimmunity and antigenic mimicry in atherosclerosis.[22,23] Heat shock protein, which plays an integral role in atherosclerosis, has been found to show strong homology between humans and CP. It has been detected in human atheroma and has lead to the concept that it could be the link between CP, arterial inflammation, and atherosclerosis.[24] It is conceivable that patients with very high titers of CPIgG represent a group with increased immune activity targeted against their endothelium, causing aggressive local inflammation leading to atherosclerosis and plaque instability. This paradigm is further supported by a study by Zhu et al,[25] which found a linear relation between coronary artery disease and IgG antibodies to an increasing number of pathogens, including cytomegalovirus, CP, hepatitis A virus, herpes simplex virus type 1, and herpes simplex type 2. Their study also showed a

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TABLE 5 Association Between IgG Antibody Titers to *Chlamydia Pneumoniae*, Inflammatory Markers, and Troponin-T

Variables	Anti-CP IgG Titers					
	<1:64 (n = 180)	1:64 (n = 30)	1:128 (n = 69)	1:256 (n = 122)	1:512 (n = 154)	≥1:1,024 (n = 241)
CRP						
Geometric mean (mg/dl)	0.50	0.52	0.54	0.45	0.40	0.41
Median (mg/dl)	0.46	0.56	0.48	0.43	0.35	0.37
Fibrinogen						
Geometric mean (mg/dl)	307.8	311.1	327	304.9	301.9	311.1
Median (mg/dl)	305.5	304	316	298	294	315
Leukocyte count						
Geometric mean (10^9/L)	7.6	7.6	7.4	7.1	7.1	7.6
Median (10^9/L)	7.3	7.5	7.6	6.8	7.1	7.4
Troponin T ≥0.2 ng/ml	30 (17%)	4 (14%)	9 (13%)	12 (10%)	20 (13%)	30 (12%)

p = NS.

similar linear relation between mean CRP levels and pathogen burden, further supporting the importance of immunologic and inflammatory response vis a vis infective agents and coronary artery disease.

Although mere seropositivity to CP has not been shown to directly correlate with the extent of atherosclerosis and its complications,[5–7,26] patients with very high antibody titers have not been specifically evaluated. The present study points toward such an association in these patients. This group might represent a different population in terms of its vulnerability to ACS.

In terms of therapeutic interventions, it appears that anti-infective therapies may need to be targeted to patients with very high antibody titers. The trials that are aimed at patients with low titer seropositivity (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders)[27] and all patients without regard to their titers (Azithromycin, and Coronary Events Study),[28] may dilute the effect of therapy. Also, given the significant role of immunologic and inflammatory processes in ACS, there might be a role for therapies aimed at modulating these resposes.

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